Brain Injury, Month?? 2008; ??(?): 1–8

informa
healthcare

A brief neuropsychological screening test battery for cognitive dysfunction in Brazilian multiple sclerosis patients

MARCO AURÉLIO NEGREIROS[1], PAULO MATTOS[1], RENATA ALVES PAES[2], J. LANDEIRA-FERNANDEZ[3], & REGINA PAPAIS ALVARENGA[2]

[1]*Instituto de Psiquiatria,* [2]*Departamento de Neurologia, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, and* [3]*Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro, Rio de Janeiro, Brazil*

(Received 7 June 2007; accepted 19 February 2008)

Abstract

Primary objective: The cognitive profile of patients with Multiple Sclerosis in the Brazilian population is relatively unknown and no cognitive screening instruments have been developed for this population. The purpose of the present study was to develop a neuropsychological screening instrument battery to identify cognitive impairment in epidemiological research protocols in this country.

Methods and procedures: Fifty-four patients with Relapsing-Remitting Multiple Sclerosis (RRMS) and 54 controls matched by sex, age and educational level were evaluated through a long and comprehensive neuropsychological test battery.

Main outcomes and results: In comparison to the control group, 51.8% of the patients with RRMS presented some form of cognitive impairment. Three neuropsychological tests—Verbal Fluency, *Rey Auditory* Verbal Learning and Enhanced Cued Recall—presented an 80.6% sensitivity and 97.2% specificity in differentiating RRMS patients with cognitive deficits from paired control subjects.

Conclusions: These three tests constitute a Brief Battery that represents a first Brazilian MS cognitive screening instrument. However, further validation study is necessary to achieve better normative scores in a larger sample and to establish feasibility of this battery.

Keywords: *Multiple sclerosis, cognition, cognitive screening, cross-cultural studies*

Introduction

Multiple Sclerosis (MS) is an inflammatory, demyelinating and idiopathic disease of the central nervous system with a chronic and progressive course [1]. The disease affects young adults with typical central nervous systems symptoms, i.e. motor, sensitivity, brainstem, cerebellar, sphincter and mental (cognitive and emotional) dysfunctions [2]. There are three main clinical MS sub-types: Relapsing-Remitting (RR), Primary Progressive (PP) and Secondary Progressive (SP). Each of them have different clinical [3], physiopathological [4] and cognitive [5–7] profiles.

Neuropsychological studies estimated that ~40–60% of MS patients present some sort of cognitive impairment [8–10]. The most common cognitive deficits are seen in attention, episodic memory, speed of information processing and executive functions. General intelligence, language and semantic memory are usually spared, highlighting a pattern of subcortical cognitive dysfunction [6,10–21], although cortical pathologies have been also associated with cognitive impairment in MS [4,22,23].

Cognitive deficits have a major impact on patient's quality of life. They can cause high rates of unemployment, difficulties with household tasks

Correspondence: Marco Aurélio Negreiros, Psychiatry, Rua Rita Ludolf 17/202, Rio de Janiero 22440-060, Brazil. E-mail: marconegreiros@superig.com.br

ISSN 0269–9052 print/ISSN 1362–301X online © 2008 Informa UK Ltd.
DOI: 10.1080/02699050801998243

and social interaction problems [13,24–26]. Depression and fatigue are frequent but their relationships to cognitive dysfunctions are not consistent. Depression as well as cognitive dysfunction seems to be a result of subcortical lesions [11,27].

The clinical neurological evaluation, as well as other common measures such as the Expanded Disability Status Examination Scale (EDSS) [2] or the Mini-Mental Status Examination (MMSE) [28] are usually unable to detect the mild cognitive deficits in MS patients [10,16,29–31]. Neuropsychological tests have been shown to be the best instruments for evaluating cognition in MS and a large number of neuropsychological test batteries have been developed for this purpose [10,29,32–34].

Cross-cultural differences are considered to be an important issue in any research that deals with cognition assessment and neuropsychological evaluation [35–37]. In this regard, there are very few data available on cognitive impairment among Brazilian MS population. In fact, only one study [38] has been carried with 25 Brazilian RRMS patients. According to this study, patients' general intelligence was well-preserved but a low performance was observed in verbal and visual long-term memory tests as well as in time-based tasks. A tendency towards depression, but not in anxiety, was also observed. Unfortunately, this study did not attempt to develop a brief cognitive test battery for screening purposes.

In the present paper, the cognitive profile of a Brazilian RRMS patients sample was investigated with a long and comprehensive neuropsychological battery. Based on this profile, a brief neuropsychological screening battery with the ability to identify cognitive deficits among this population is proposed. The main goal is to use this instrument in research protocols in order to investigate epidemiological prevalence of cognitive impairment in the MS population. Furthermore, after a validation study, this screening battery can be incorporated in clinical practice as the starting point of reference for a comprehensive neuropsychological evaluation.

Method

Participants

Patients were consecutively admitted for neurological assistance at the Demyelinating Disease Sector at Lagoa Hospital in Rio de Janeiro. All patients were diagnosed with RRMS according Poser's criteria [39] for clinically-defined MS and having mild-to-moderate levels of impairment (1–6.5) in the Expanded Disability Status Scale–EDSS [2]. Four excluding criteria were employed in order to prevent possible interferences in neuropsychological test performance: (1) presence of visual or motor deficits that compromise adequate response on cognitive tests; (2) state of acute bout or worsening of the symptoms; (3) use of psychoactive substances other than prescribed anti-depressants; and (4) co-existent clinical conditions (clinical depression, thyroid alterations, systemic high blood pressure, HIV, syphilis and other neurological and psychiatric diseases) that interferes with cognition. All patients underwent standard medical and psychological interview, analyses of the medical records, neurological examination, MRI exam and cerebral spinal fluid investigation, in order to fulfil the above criteria.

Healthy adult subjects matched to RRMS patients according to their sex, age and education level were employed as a paired control group. They were recruited among relatives and friends of the medical team of the hospital. The same interview applied to patients was conducted in order to exclude healthy participants who had a history of substance abuse or were currently using psychoactive substances. Participants who presented neurological, psychiatric or any other disorder that could potentially affect cognition were excluded from the control group.

Measures

Table I show the neuropsychological battery employed in the present study. Dementia screening was performed by the Memory-Information-Concentration test (MIC) [40] which has several advantages over the MMSE since it does not contain visual or motor tasks [28]. Attention and speed of information processing were evaluated by the Digit Symbol-Oral version [16,41]. It was decided to employ this test (and not 'gold-standard' Symbol Digit Modality [20]) because it is based on the graphic equivalent of the WAIS III Battery and was adapted by this group to eliminate the motor aspect in response performance [16]. Attention span and working memory were assessed by the Digit Span Forward and Backward, respectively (WAIS III Battery) [41].

The *Rey Auditory* Verbal Learning test (RAVLT) [42] was employed to measure long-term verbal memory. One phase of late free recall and another one related to recognition were included so that these two memory processes could also be evaluated. Long-term memory was also accessed by the Buschke Enhanced Cued Recall Test (BECR) [43]. This is an important test since it evaluates simultaneously verbal and non-verbal memory, long-term memory with the aid of semantic clues

during the recall period. Verbal fluency was tested by the Controlled Verbal Oral Association test (COWAT). This is a measure of verbal output and executive function which include Phonetic (F.A.S.) and Semantic (animals and fruits) words [44]. Finally, abstract thinking was evaluated through the Raven Progressive Matrices [45]. To reduce a fatigue effect and avoid testing time period, only series A and C of the original form of this test were employed.

Data analysis

Results are presented as means and their respective standard error ($\pm$SEM). A two-tail student *t*-test was employed to detect mean significant differences between RRMS and control groups among the 26 cognitive variable indices. The chi-square test was used to identify percentage differences between the two groups. A Pearson correlation analysis was used to assess the relationship between cognitive deficit among the MS patients and the severity of the disease according to the Expanded Disability Status Scale (EDSS). A *p*-value of 0.05 was considered statistically significant.

Cognitive dysfunction was defined according to the procedure employed by Rao et al. [10], which controls for eventual individual differences in pre-morbid cognitive abilities. A multiple regression was performed with the raw score for each of the 26 cognitive indices as the dependent variable and the demographic variables (sex, age and level of education) as the independent variables. Since sex is not a continuous variable, it was regressed as a dummy variable. A standardized residual was obtained by subtracting the regressed and the actual scores of each of the 26 variable indices. Failure in each of these variables was defined as the fifth percentile or below of the standardized residual score among the paired control subjects.

Cognitive deficit among RRMS patients was defined as the fifth percentile of the total number of failed cognitive indices of the control subjects. The frequency rate of cognitive dysfunction in this RRMS patient sample was calculated as the difference between the percentages of RRMS patients who presented cognitive deficit from a false positive rate defined as the percentage of paired control subjects misclassified as cognitively impaired. In order to build a brief cognitive battery to screen MS patients with cognitive dysfunctions, sensitivity of the 26 variable across the different neuropsychological tests was determined by the percentage of RRMS patients who failed each of these indices.

Results

Twenty patients from a total of 74 initially selected were excluded: six did not fulfil diagnostic criteria, five had EDSS higher than 6.5, three were using psychoactive substances, one presented acute bout and five did not complete the assessment process. Therefore, the final sample of this study was composed of 54 RRMS patients and 54 paired control healthy subjects.

Table II presents the percentage and the mean of the SEM of the demographic variables of the RRMS and control samples. There were no differences between age, education and gender distribution between the two groups (all p's > 0.1). Results indicate that the incidence of RRMS in this sample was greater in females (61.1%) than in males (38.9%; $\chi^2 = 7.1$, $p < 0.05$). Table II also presents the total amount of failed indices among the 26 cognitive variable indices. MS patients presented a greater number of failed indices as compared to paired control subjects ($t_{104} = 6.67$; $p < 0.001$).

Employing a cut-off of four or more failed cognitive indices (nine-fifth percentile of the failed tests among control subjects) an incidence of 59.2% of RRMS patients and 7.4% of control subjects

Table I. Neuropsychological tests.

Cognitive function	Neuropsychological test
Dementia Screening	Memory-Information -Concentration (MIC)
Attention/Concentration	Digit Symbol
Memory	
Short-term	Digit Span (forward and backward)
Long-term	Rey Auditorial Verbal Learning Test(RAVL)
	Buschke Enhanced Cued Recall Test (BECR)
Verbal Fluency	Controlled Oral Word Association Test (COWAT) Phonetic: F-A-S Semantic: Animals & Fruits
Abstract Thinking	Raven Progressive Matrices

Table II. Percentage and mean with the standard error of the mean in parenthesis of the demographic variables (sex, age and level of education) and general cognitive performance (total of failed cognitive indexes) among multiple sclerosis and healthy control subjects.

Group	Male	Age	Education	Foiled tests
Multiple Sclerosis	38.9%	38.7 (1.4)	11.7 (0.5)	5.4 (0.5)
Paired Controls	35.2%	35.0 (1.7)	11.8 (0.5)	1.3 (0.2)

Table III. Mean (SEM) of the 26 cognitive indexes tests among MS patients and healthy control subjects. The *p*-value of the two-tailed *t*-test comparison between the two groups, the percentage of MS patients below the fifth percentile of the control group (%MS < 5%ile) and the order of placements of all these percentage are also presented.

Cognitive test	RRMS	Paired control	*P*	% RRMS <5%ile	Order
Dementia Screening					
MIC	2.44 (0.40)	1.23 (0.26)	<0.014	9.3%	21°
Attention/Concentration					
Digit Symbol	44.37 (1.04)	52.81 (1.23)	<0.001	22.2%	12°
Memory					
Short-term					
Digit Span					
Foward	5.92 (0.15)	6.57 (0.18)	<0.008	11.1%	20°
Backwards	3.87 (0.15)	4.48 (0.21)	<0.018	7.4%	22°
Long-term					
RAVL					
RAVLT 1	5.10 (0.20)	6.24 (0.23)	<0.001	27.8%	8°
RAVLT 2	7.72 (0.33)	8.67 (0.34)	<0.05	3.7%	23°
RAVLT 3	9.07 (0,35)	10.48 (0.34)	<0.005	22.2%	12°
RAVLT 4	10.10 (0.37)	11.46 (0.31)	<0.007	18.5%	18°
RAVLT 5	10.64 (0.34)	12.39 (0.30)	<0.001	22.2%	12°
RAVLT - Recall 1	7.56 (0.45)	10.39 (0.34)	<0.001	33.3%	5°
RAVLT - Recall 2	8.02 (0.44)	10.50 (0.38)	<0.001	35.2%	3°
RAVLT - Recog	27.29 (0.30)	28.63 (0.21)	<0.001	35.2%	3°
BECR					
Free 1	10.22 (0.30)	12.34 (0.26)	<0.001	29.6%	6°
Free 2	11.63 (2.12)	13.18 (0.26)	<0.001	0.0%	24°
Free 3	12.11 (0.30)	14.16 (0.21)	<0.001	20.4%	17°
Cued 1	5.44 (0.25)	3.66 (0.26)	<0.001	0.0%	24°
Cued 2	4.15 (0.26)	2.78 (0.26)	<0.001	27.8%	8°
Cued 3	3.72 (0.27)	1.74 (0.21)	<0.001	0.0%	24°
BECR-Recall	47.27 (0.21)	47.94 (0.04)	<0.002	29.6%	6°
BECR-Recog	47.61 (0.12)	47.96 (0.03)	<0.002	22.2%	12°
Verbal fluency					
COWAT phonetic					
Letter "F"	11.88 (0.58)	15.88 (0.67)	<0.001	22.2%	12°
Letter "A"	10.83 (0.48)	14.14 (0.63)	<0.001	25.9%	11°
Letter "S"	10.02 (0.55)	14.48 (0.65)	<0.001	40.7%	1°
COWAT semantic					
Animals	16.35 (0.56)	19.61 (0.73)	<0.001	18.5%	18°
Fruits	14.11 (0.45)	17.53 (0.57)	<0.001	40.7%	1°
Abstract thinking					
Raven	16.89 (0.55)	18.70 (0.58)	<0.02	27.8%	8°

with cognitive impairment was found. Therefore, a frequency rate of cognitive impairment in this sample was estimated in 51.8%. Interestingly, no correlation between cognitive deficit among the RRMS patients and the severity of the disease (EDSS) was found ($r = 0.03$, $p > 0.8$).

Table III depicts the mean (SEM) of each of the 26 cognitive indices tests among RRMS patients and paired control subjects. A two-tailed *t*-test comparison between the two groups indicated that RRMS patients consistently presented lower performance than control subjects (all p's < 0.05) in all 26 indices. Table III also presents the percentage of RRMS patients below the fifth percentile of the control group and the sensitivity order of placements of all these percentages. Phonetic and semantic verbal fluency were the most sensitive cognitive variables. About 40% of the RRMS patients presented a deficit in generating words that start with the letter 'S' (phonetic) or fruit words (semantic). These two indices were not redundant since half of RRMS patients who presented a failure in generating fruit words did not present any deficit in generating words staring with the letter 'S'.

Long-term memory as measured by RAVLT also demonstrated a high level of sensitivity. As can be observed in Table III, 35.2% of the RRMS patients presented a failure in the RAVLT second recall and recognition tests, whereas 33.3% of the patients failed the first recall in the RAVLT. A considerable overlap between the first and the second recall in the RAVLT in the performance among RRMS patients was detected. Only 17% of the patients who failed

Table IV. Sensitivity and specificity of three brief cognitive test batteries in predicting the cognitive deficit detected with a much more complex neuropsychological test battery described in Table I.

	One or more test impaired		Two or more test impaired	
Predictor tests	Sensitivity	Specificity	Sensitivity	Specificity
Battery 1	77.8%	84.7%	30.6%	100%
Battery 2	88.9%	79.2%	66.7%	98.6%
Battery 3	100%	73.6%	80.6%	97.2%

the first RAVLT recall performed well in the second RAVLT recall. Conversely, there was no redundancy between the RAVLT second recall and the recognition tests. This is due to the fact that 42% of the RRMS patients who failed to evoke did not present any deficit in the recognition test.

Assessment of long-term memory including BECR also demonstrated considerable cognitive deficit sensitivity among MS patients. Approximately 30% of the patients presented a failure in the first free recall trial of the BECR (BECR–Free 1) and during total recall (48 points) of the BECR (BECR–Recall). These two indices were not redundant since ~ 58% of the RRMS patients who presented a deficit in the first free recall trial performed well during the BECR recall.

In order to develop an instrument that could reliably predict the cognitive deficits observed among the RRMS patients, sensitivity and specificity rates of three brief test batteries were determined. These batteries included the most sensitive indices of the extensive neuropsychological testing: Letter 'S' and fruit words from Verbal Fluency; Recall 2 and Recognition from RAVLT; Free Recall 1 and Recall from BECR. These results are presented in Table IV.

Battery 1 included the Letter 'S' and Fruit words indices from the COWAT. Battery 2 was composed of all the variables in Battery 1 plus the Recall-2 and Recog indices from RAVLT. Battery 3 was composed of all the variables in Battery 2 plus Recall Free-1 and Total Recall indices from BECR. Classification of the RRMS patients with a cognitive deficit in each of these three brief batteries occurred according to two cut-off criteria: a lenient method, which consisted of one or more impaired cognitive index, and a more conservative method, which consisted of two or more impaired cognitive indices. The more conservative cut-off led to high specificity (97.2–100%), but low sensitivity (30.6–80.6%). In contrast, the more lenient cut-off resulted in higher sensitivity (77.8–100%) and acceptable levels of specificity (73.6–84.7%).

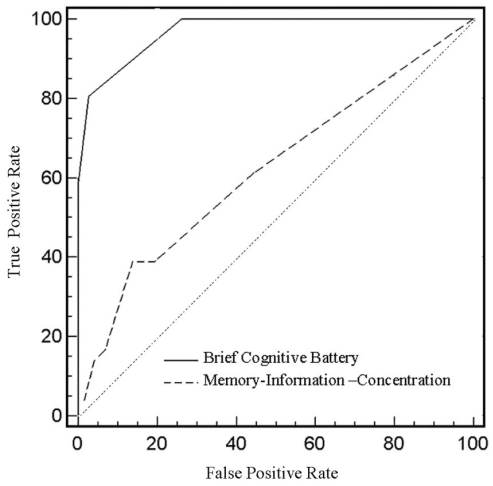

Figure 1. ▮▮▮▮.

Receiver operating characteristic (ROC) curves for Battery 3 and the Memory-Information–Concentration Test (MIC) are presented in Figure 1. The diagonal across the graph indicates that the instrument does not have any discrimination ability since its false and true positive rates have the same value. The more the curve departs from the diagonal, the better its discriminating ability. As can be observed in Figure 1, the brief cognitive battery with four indices from three different tests (COWAT, RAVLT and BECR) presented a much better ability to discriminate RRMS patients with cognitive deficits when compared with the MIC.

Discussion

The present results indicated that more than half of the sample of RRMS patients presented some sort cognitive impairment as assessed by a long and comprehensive neuropsychological evaluation. This result is in conformity with previous studies reported in the literature which indicated that ~40–60% of MS patients have cognitive deficits detected through neuropsychological testing [8–10].

The screening tests for dementia (MIC) and the attention and concentration measures (Digit Span) indicated that 9.3% and 11.1% of these RRMS patients presented a failure in each of these tests, respectively. These results are somewhat divergent from reports in the literature which indicated that MS patients have preserved attention span and a smaller dementia scores [10,11,20]. Abstract thinking deficits detected in 27% of the patient sample, as well as the difference found in the

performance tests for verbal fluency between patients and paired control subjects, may be attributed to frontal executive dysfunction described as an integrating part of MS's cognitive physiopathology [11,46,47].

The slowness in the speed of information processing is considered to be one of the main characteristics in the MS cognitive disorder [25,48,49]. This deficit has been pointed out to be one of the most sensitive measure for detecting cognitive disorders [50] and the main cognitive function affected in MS patients [51]. It has been also argued that deficits in working memory [52] and executive functions are the most fundamental features of cognitive disorder in MS [19,46]. The present results indicated that a deficit in executive function, measured through RAVEN and COWAT conjointly, is in fact an important feature among RRMS patients. The high frequencies of deficits in these tests are in agreement with the above-mentioned studies, which relate cognition in MS to a sub-cortical frontal executive disorder.

The present results also indicated that recent memory is significantly impaired in all stages (learning, recall and recognition) in the RAVLT and BECR tests. The range of recent memory impairment was between 18.5–29.6% of patients. Late recall processes were very affected as measured by RAVLT–recall 1 and 2 and BECR-recall. Recall deficit in all these measures were fairly high, in the range of 30–35%. Interesting, RRMS patients presented a 22% and 35% deficit in the RAVLT–recognition and BECR–recognition tests, respectively. These results are not in accordance with the classical view that assumes that recognition memory is preserved in MS patients [11,53,54]. A problem in encoding mechanism in the RRMS patient sample could explain this particular finding. This possibility is corroborated by the fact that this sample also presented a high impairment in generative verbal fluency. However, additional studies are essential to further investigate this possibility. The relatively small number of subjects of the present study can lead to a false positive cognitive deficit identification. Although a conservative statistical method was considered to define cognitive impairment, further study must be made in a larger sample.

A number of screening batteries have been proposed to identify cognitive dysfunction in MS [10,29–31]. One classical study [10] led to construction of the Brief Repeatable Neuropsychological Battery (BRB-N). This battery is widely employed but it was constructed without disease's clinical subtype specificity. In fact, recent results indicated different profiles of cognitive alterations in each clinical type of MS [5,7,52]. The present results indicated that a brief neuropsychological battery composed by the COWAT, the Verbal Semantic Fluency (letter 'S' and 'Fruits'), the BECR and the RAVLT might be useful for cognitive impairment screening among the Brazilian RRMS sub-type. This brief battery presented high sensitivity and specificity in differentiating RRMS patients with cognitive deficits from paired control subjects.

Since this is a first attempt to develop a brief neuropsychological screening test for cognitive deficits in Brazilian MS patients, subsequent studies are important to evaluate its validity. In addition to that, more systematic comparisons with other screening instruments described in the literature are necessary as well.

Finally, it is important to emphasize that, although a screening instrument is very useful for research, it should not substitute clinical judgement and the relevance of a comprehensive neuropsychological evaluation, crucial for proper management of the serious impact of cognitive dysfunction on the daily life activities of MS patients.

Acknowledgement

MAN had a CAPES doctoral fellowship. RAP has a CAPES master fellowship. JLF is supported by CNPq grant 522720-95-1.

References

1. Kantarci OH, Weinshenker BG. Natural history of multiple sclerosis. Neurological Clinics 2005;23:17–38.
2. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
3. Matthews EB. Clinical Aspects. In: Compston DAS, editor. McAlpine's multiple sclerosis. London: Churchill Livingstone; 1998. pp 43–251.
4. Kutzelnigg A, Lucchinetti CF, Stadelmann C, Brück W, Rauschka H, Bergmann M, Schmidbauer M, Paresi JE, Lassmann H. Cortical demylination and diffuse white matter injury in MS. Brain 2005;128:2705–2712.
5. Gaudino EA, Chiaravalloti ND, Deluca J, Diamond BJ. A comparison of memory performance in relapsing-remitting, primary progressive and secondary progressive, multiple sclerosis. Neuropsychiatry, Neuropsychology and Behavioral Neurology 2001;14:32–44.
6. Hutchinson J, Burke ▮▮, Hutchinson M. Neuropsychological assessment in multiple sclerosis: Methodological issues and concerns. Multiple Sclerosis 1996;2:57–65.
7. Zakzanis KK. Distinct neurocognitive profiles in multiple sclerosis subtypes. Archives of Clinical Neuropsychology 2000;15:115–136.
8. Rao SM. Neuropsychology of multiple sclerosis. Current Opinion in Neurology 1995;8:216–220.
9. Rao SM. Neuropsychological screening battery for multiple sclerosis. Milwaukee: Medical College of Wisconsin; 1991.

10. Swirsky-Saccheti TS, Mitchell DR, Seward J, Gonzales C, Lublin F, Knober R, Field HL. Neuropsychological and structural brain lesion in multiple sclerosis: A regional analysis. Neurology 1992;42:1291–1295.
11. Beatty WW. Cognitive and emotional disturbances in multiple sclerosis. Neurology Clinics 1993;11:189–204.
12. Beatty WW, Monson N. Metamemory in multiple sclerosis. Journal of Clinical and Experimental Neuropsychology 1991;13:303–327.
13. Bobholz JA, Rao SM. Cognitive dysfunction in multiple sclerosis: A review of recent developments. Current Opinions in Neurology 2003;16:283–288.
14. Kujala P, Portion R, Rumatianimen J. Memory deficit and early cognitive deterioration in MS. Acta Neurologica Scandinavica 1996;93:329–335.
15. Negreiros MAGM, Colin DD, Mattos PM, Papais-Alvarenga RM. FS Mental no EDSS: Dificuldades no estadiamento cognitivo da esclerose múltipla. Arq Neuropsiquiatr 1996;54(suppl):531.
16. Negreiros MAGM, Papais-Alvarenga RM, Mattos PE. Alterações Neurocognitivas na Esclerose Múltipla: Resultados de primeiro estudo piloto. Arq Neuropsiquiatr 1996;54(suppl):97.
17. ▮▮▮▮.
18. Peyser JM, Edwards KR, Poser CM. Cognitive functions in multiple sclerosis. Archives of Neurology 1980;37:577–579.
19. Rao SM. White matter disease and dementia. Brain Cognition 1996;31:250–268.
20. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis I: Frequency, patterns and prediction. Neurology 1991;41:685–691.
21. Barget B, Camplais P, Borudette D. Cognitive dysfunction in multiple sclerosis: Natural history, pathophysiology and management. CNS Drugs 2002;16:445–455.
22. Portaccio E, Amato MP, Bartolozzi ML, Zipoli V, Mortilla M, Guidi L, Siracusa G, Sorbi S, Federico A, De Stefano N. Neocortical volume decrease in relapsing-remitting multiple sclerosis with mild cognitive impairment. Journal of Neurological Science 2006;245:195–199.
23. Morgen K, Sammer G, Courtney SM, Wolters T, Melchior H, Blecker CR, Oschmann P, Kaps M, Vaitl D. Evidence for a direct association between cortical atrophy and cognitive impairment in relapsing-remitting MS. Neuroimage 2006;30:891–898.
24. Amato MP, Ponziani G, Pracucci G, Bracco L, Siracusa G, Amaducci L. Cognitive impairment in early-onset multiple sclerosis: Pattern, predictors, and impact on everyday life in a 4-year follow-up. Archives of Neurology 1995;52:168–172.
25. Benedict RHB, Carone DA, Bakshi R. Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis. Journal of Neuroimaging 2004;14:36S–45S.
26. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis II: Impact on employment and social functioning. Neurology 1991;41:692–696.
27. Arnett PA, Higginson CI, Randolph JJ. Depression in multiple sclerosis: Relationship to planning ability. Journal of the International Neuropsychology Society 2001;7:665–674.
28. Folstein MF, Folstein S, McHugh PR. 'Mini-Mental State'. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychology Research 1975;12:189–198.
29. Basso MR, Hazen SB, Lynn JRK, Barstein RA. Screening for cognitive dysfunction in multiple sclerosis. Archives of Neurology 1996;53:980–984.
30. Beatty WW, Goodkin DE. Screening for cognitive impairment in multiple sclerosis: Evaluation of the Mini-Mental State Examination. Archives of Neurology 1990;47:p 297.
31. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients: A consensus approach. Clinical Neuropsychology 2002;16:381–397.
32. Kujala P, Portion R, Revonsuo A, Rumatianimen J. Attention related performance in two cognitively different subgroup of patient with multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 1995;59:77–82.
33. Beatty WW, Paul RH, Wilbanks SL, Hames KA, Blanco CR, Goodkin DE. Identifying multiple sclerosis patients with mild or global cognitive impairment using the Screening Examination for Cognitive Impairment (SEFCI). Neurology 1995;45:718–723.
34. Franklin GM, Heaton RK, Nelson LM, Filley CM, Seibert C. Correlation of neuropsychological and MRI findings in chronic/progressive multiple sclerosis. Neurology 1988;38:1826–1829.
35. Ardila A. Directions of research in cross-cultural neuropsychology. Journal of Clinical and Experimental Neuropsychology 1995;17:143–150.
36. Luszcz M. Back to nurture: Cross-cultural research as a paradigm for understanding bio-cultural dynamics of cognitive ageing. Gerontology 2006;52:290–294.
37. Tong BS, Yip JT, Lee TM, Li LS. Frontal fluency and memory functioning among multiple sclerosis patients in Hong Kong. Brain Injury 2002;16:987–995.
38. Andrade VM, Bueno OFA, Oliveira ASB, Oliveira EML, Miranda MC. Cognitive profile of patients with relapsing remitting multiple sclerosis. Arq Neuropsiq 1999;57:775–783.
39. Poser CM, Paty SW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Annals of Neurology 1983;13:227–231.
40. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. British Journal of Psychiatry 1968;114:797–811.
41. Wechsler D. Wais-III—Escala de Inteligência Wechsler para adultos. Manual para administração e avaliação; Adaptação e padronização de uma amostra brasileira Elizabeth do Nascimento. São Paulo: Casa do Psicólogo; 2004.
42. Rey A. L'examen Clinique em Psychologie. Paris: Press Universitaires de France; 1964.
43. Buschke H. Cued recall in amnesia. Journal of Clinical Neuropsychology 1984;6:433–440.
44. Benton AL, Hamsher K. Multilingual aphasia examination. Iowa City: University of Iowa Press; 1976.
45. Raven JC. Matrizes Progressivas. Rio de Janeiro: CEPA—Centro Editor de Psicologia Aplicada; 1998.
46. Beatty WW, Monson N. Problem solving by patients with multiple sclerosis: Comparison of performance on the Wisconsin and California Card Sorting Tests. Journal of the International Neuropsychology Society 1996;2:134–140.
47. Foong J, Rozewicz L, Quaghebeur G. Executive function in multiple sclerosis. The role of frontal lobe pathology. Brain 1997;120:15–26.
48. Demaree HA, DeLuca J, Gaudino EA, Diamond BJ. Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. Journal of Neurology, Neurosurgery and Psychiatry 1999;67:661–663.

49. Sonneville LMJ, Boringa JB, Reuling IEW, Lazeron RHC, Ader HJ, Polman CH. Information processing characteristics in subtypes of multiple sclerosis. Neuropsychologia 2002;40:1751–1765.
50. Henry JD, Beatty WW. Verbal fluency deficits in multiple sclerosis. Neuropsychologia 2005;44:1166–1174.
51. Collo SLB. Quality of life in multiple sclerosis: Does information-processing speed have an independent effect? Archives of Clinical Neuropsychology 2006;21: 167–174.
52. Huijbregts SCJ, Kalkers NF, De Sonneville LMJ, De Groot V, Reuling IEW, Polman CH. Differences in cognitive impaiment of relapsing remitting, secondary, and primary progressive MS. Neurology 2004;63: 335–339.
53. Armstrong C, Onishi K, Robinson K, D'Esposito M, Thompson HRA, Grossman M. Serial position and temporal effects in multiple sclerosis: Two subtypes of defectives memory mechanisms. Neuropsychology 1996;34:853–862.
54. Thornton AE, Raz N, Tucker A. Memory in multiple sclerosis: Contextual encoding deficits. Journal of the International Neuropsychology Society 2002;8:395–409.